REMARKS

Claims 1-8 are now pending in the application. Claims 1-8 are rejected. Claims 1, 2, and 4-8 have been amended.

The Amendments

Claim 1 has been amended to provide proper antecedent support and to clarify the invention. Support can be found, for example, at page 3, line 16, and page 8, lines 5-10. Claim 2 has been amended for clarification. Support can be found, for example, at page 1, lines 21-25, and page 8, lines 5-12. Claim 4 has been amended to provide proper antecedent support. Support can be found, for example, at page 3, line 28 to page 4, line 2. Claims 5-8 have been amended to provide proper antecedent support. Support can be found, for example, at page 7, lines 15-18, page 10, lines 9-13, and page 15, lines 24-30.

Rejection of Claims Under 35 U.S.C. § 112, Second Paragraph

Claims 2, 3, and 5-8 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner states that the phrase "derivative of the second polyketide" renders claim 2 vague and indefinite because the metes and bounds of what is considered to be a derivative in this context is unclear. In addition, the Examiner asserts that there is no clear positive antecedent basis in claim 2 or claims 5-8 for the phrase "the overproducing cell." Regarding claims 5-8, the Examiner states that the amount of polyketide produced is unclear because it is unclear whether the level is relative to the medium used to culture the cell, or relative to an extract made from the cell.

Claim 2 has been amended to clarify the difference between the first and second PKS. Claim 1 has been amended to include the phrase "an overproducing cell." Claims 5-8 have been amended to clarify that the amount of polyketide produced is measured in grams per liter of culture medium.

Accordingly, Applicant asserts that the language of claims 2, 3, and 5-8 are clear and meet the requirements of 35 U.S.C. § 112, second paragraph.

Rejection of Claims Under 35 U.S.C. § 102(b)

Claims 1-4 and 7-8 stand rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,672,491 (hereinafter "the '491 Patent").

The Examiner asserts that the '491 Patent teaches a method of producing a new polyketide by deleting the entire natural PKS gene cluster of a cell that is optimized to produce a polyketide, and then introducing a functional PKS gene set into the cell, which then produces the new polyketide.

As amended, claim 1 describes a method for producing a first polyketide, said method comprising expressing polyketide synthase (PKS) genes encoding a first PKS that produce the first polyketide in an overproducing cell that has been optimized to express polyketide synthase (PKS) genes encoding a second PKS that produces a second polyketide, wherein the genes encoding the second PKS are deleted or otherwise rendered inactive. Overproducing host cells are disclosed in the subject application at page 5, line 16, to page 8, line 4. In contrast, the '491 patent does not describe the use of an overproducing cell that has been optimized for the production of a second polyketide, to produce a first polyketide.

The '491 patent teaches a genus of cells that are capable of expressing a polyketide synthase (PKS) gene cluster. The fact that the '491 patent does not specifically refer to the subset of overproducing cells that are claimed in the subject application, does not preclude patentability of the species. The attention of the Office is called to the decision in *Integra Lifesciences v. Merck*, 331 F.3d 860; 2003 U.S. App. LEXIS 11335; 66 U.S.P.Q.2D (Fed.Cir. 2003) which provides guidance as to the general teachings of such genus-species relationships. In that case, claims to a cyclic peptide were found to be patentable over a patent that disclosed but did not specifically claim cyclic RGD peptides. A copy of this case is included with the Response.

For the reasons presented above, Applicant asserts that claims 1-4 and 7-8 are patentable under 35 U.S.C. § 102(b) over the '491 Patent.

Rejection of Claims Under 35 U.S.C. § 103(a)

Claims 1-8 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over the '491 patent in view of U.S. Patent No. 6,177,262 (hereinafter "the '262 Patent").

The '491 is cited by the Examiner as teaching as described above, and also as not teaching the method of producing a first polyketide in which the cell overproduces the second polyketide at a level greater than 10 g/L. The '262 Patent is cited by the Examiner as teaching increasing the yields of polyketides produced in host cells by coexpression of the ptpA gene. In addition, the Examiner states that the '262 Patent teaches ptpA coexpression strains that produce over 10 g/L of polyketides (column 13). The Examiner also states that it would have been obvious to one skilled in the art to use the cells that coexpress the ptpA gene (and which produce a polyketide) taught by the '262 Patent, as the cells used in the method of producing a polyketide as taught by Khosla.

The '491 has been discussed *supra*. In addition, the '262 Patent does not remedy any of the deficiencies of the '491 Patent.

Applicant requests clarification from the Examiner regarding his characterization of the '262 Patent as teaching ptpA coexpression strains that produce over 10 g/L of polyketides (column 13). Nowhere in column 13 is there a description of a polyketide being produced in the quantity of over 10 g/L.

According to the MPEP § 2142, three criteria must be met to establish a *prima facie* case of obviousness. (a) there must a suggestion and motivation to modify or combine reference teachings; (b) there must be a reasonable expectation of success, and (c) the cited references must teach or suggest all the claimed limitations.

[01] First, there is no suggestion or motivation in either reference to produce a first polyketide, by expressing polyketide synthase (PKS) genes encoding a first PKS that produce the

first polyketide in an overproducing cell that has been optimized to express polyketide synthase (PKS) genes encoding a second PKS that produces a second polyketide, wherein the genes encoding the second PKS are deleted or otherwise rendered inactive. Second, even if the '491 Patent and the '262 Patent did suggest what the Applicant has claimed, there is no reasonable expectation that the result would be successful. As described in the specification at page 6, line 3, *et seq.*, surprisingly little has been reported about the determinants of overproduction in industrial microorganisms. The biochemical reasons for such overproduction are often difficult to determine. Several different reasons for overproduction of a polyketide can exist: mutations in biosynthetic enzymes that increase flux; up-regulation of corresonding gene expression; higher intracellular pools of substrates; or mutations in the PKS genes themselves. Thus, even if the cells described in the '262 patent were used as overproducing cells in the method of the '491 patent, there is no reasonable expectation that overproduction of a polyketide would result. Third, the cited references do not teach or suggest all the claimed limitations.

In conclusion, Applicants asserts that claims 1-8 are patentable under 35 U.S.C. § 103(a) over the '491 Patent in view of the '262 Patent

CONCLUSION

In view of the above remarks and arguments, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 300622005400.

Dated: August 25, 2003

Respectfully submitted,

By Brenda J Wallach

Brenda J. Wallach, Ph.D.
Patent Agent
Registration No.: 45,193
MORRISON & FOERSTER LLP
3811 Valley Centre, Suite 500
San Diego, California 92130
(858) 720-5100